REMARKS

Claims 1 and 2 have been amended. No new matter has been added. Support for the claim amendments may be found throughout the specification, for example, at page 9, paragraph 2 of the specification.

Applicants thank the Examiner for withdrawing the previous rejections.

Claims 1, 2 and 5-16 are pending.

CLAIM REJECTIONS

Rejection of claims under 35 U.S.C. 103

Nishikawa

The Examiner has rejected claims 1, 2, 5-8, 10 and 12-16 under 35 U.S.C. § 103(a) as being unpatentable over Nishikawa et al. (*Development*, 1998; Vol. 125, p. 1747-1757) ("Nishikawa"). See Office Action at p. 3. Claims 5-8, 10 and 12-16 depend from independent claim 1 and 2.

Claim 1 relates to a method for determining the effect of a plurality of culture conditions on a cell that includes the steps of: (a) providing a first set of groups of cell units each including one or more cells, and exposing the groups to desired culture conditions, (b) subdividing one or more of the groups to create a further set of groups of cell units, (c) exposing the further groups to at least one change of culture conditions, (d) repeating steps (b)-(c) iteratively and (e) assessing the effect on a given cell unit of the culture conditions to which it has been exposed. Claim 2 relates to a method for determining the effect of a plurality of culture conditions on a cell, that includes the steps of a) providing a first set of groups of cell units each including one or more cells, and exposing the groups to desired culture conditions, (b) pooling two or more of the groups to form at least one second pool, (c) subdividing the second pool to create a further set of groups of cell units, (d) exposing said further groups to at least one change of culture conditions, (e) repeating steps (b)-(d) iteratively and (f) assessing the effect on a given cell unit of the culture conditions to which it has been exposed.

Nishikawa describes that "CCE ES cells ... were initially maintained in Mitomycin C ... treated embryonic fibroblast layers in Dulbecco modified essential medium (DMEM: Gibco) ...." See p. 1748. Nishikawa further describes transferring ES cells "to gelatin (Sigma, USA)-coated culture dishes to remove fibroblasts." Id. Nishikawa also states that "10^4 ES cells were

then transferred to each well of type IV collagen-coated 6-well cluster dishes ... and incubated in a-MEM supplemented with 10% FCS and $5X10^{-5}$M 2ME." Id. Nishikawa then describes harvesting the cells and analyzing cells for surface markers. Id. In preliminary experiments, cells were grown in dishes coated with different factors and the ability of these to support the differentiation of ES cells into $FLK1^+$ cells was assessed. Id. In addition, in order to culture cells that were both $FLK1^+$ and $cadherin^+$, cells were grown with a mixture of recombinant growth factors. Id. Contrary to the Examiner's position, Nishikawa does not disclose repeating steps (b) and (c) or (d) iteratively nor does Nishikawa disclose a single round of steps (b) and (c) or (d) of claim 1 or claim 2.

As can be seen from Nishikawa, the initial step of growing the ES cells on mitomycin C treated embryonic fibroblasts layers is undertaken to maintain the cells as ES cells and not as part of a method for determining the effect of a plurality of culture conditions on a cell (see p. 1748). Furthermore, as indicated by the final paragraph in the left-hand column on page 1748, the transfer of the ES cells to gelatin is undertaken to remove fibroblasts and as such, cannot in any way be considered to be part of a method as claimed in claims 1 or 2 because this transfer is not directed towards a method for determining the effects of culture conditions on a cell. This transfer step is merely directed towards producing cells which are suitable as the starting material for subsequent use in Nishikawa. This position is further supported by the first sentence in the right-hand column of page 1748 which indicates that following the transfer of cells to gelatin-coated culture dishes, the cells are still considered to be ES cells. These ES cells are then transferred to type IV collagen coated 6-well culture dishes. Id.

The skilled person viewing Nishikawa would understand that it is these ES cells which must be considered to be the first set of cell units referred to in step (a) of claim 1. The cells are then exposed to medium comprising a-MEM supplemented with 10% FCS and 2 ME. Id. Subsequently these cells are analyzed for the expression of surface markers. Id. In a different experiment, the cells were incubated in medium containing a mixture of recombinant growth factors. Id. Therefore, Nishikawa does not only not disclose repeating the steps of claim 1 or claim 2 iteratively, but does not even disclose the step of sub-dividing one or more of said groups to create a further set of groups of cell units which are subsequently exposed to at least one change of culture conditions.

As such, Nishikawa does not teach or suggest a method for determining the effect of a plurality of culture conditions on a cell that includes the steps of: (a) providing a first set of groups of cell units each including one or more cells, and exposing the groups to desired culture conditions, (b) subdividing one or more of the groups to create a further set of groups of cell units, (c) exposing the further groups to at least one change of culture conditions, (d) repeating steps (b)-(c) iteratively and (e) assessing the effect on a given cell unit of the culture conditions to which it has been exposed. Nishikawa further does not teach or suggest a method for determining the effect of a plurality of culture conditions on a cell, that includes the steps of a) providing a first set of groups of cell units each including one or more cells, and exposing the groups to desired culture conditions, (b) pooling two or more of the groups to form at least one second pool, (c) subdividing the second pool to create a further set of groups of cell units, (d) exposing said further groups to at least one change of culture conditions, (e) repeating steps (b)-(d) iteratively and (f) assessing the effect on a given cell unit of the culture conditions to which it has been exposed.

Furthermore, Applicants would like to respectfully point out that contrary to the Examiner's assertions, it would not be obvious to one of ordinary skill in the art to modify the teaching of Nishikawa to result in a method which includes repeating steps corresponding to steps (b) and (c) or (d) of amended claim 1 or 2 iteratively.

It is anything but clear that repeating the step of growing the cell on the coated plate would result in a further effect on the cell and so the skilled person would consider this to be an unnecessary extra step which would simply result in an increased number of samples and thus more work for which there is no motivation. Therefore, the person of ordinary skill in the art viewing Nishikawa would have no motivation to subdivide the cells and repeat the step of growing the cells on the coated plates as this would likely merely result in the production of the same cell type. There is no motivation to do this when the methods described in Nishikawa are already described as being effective. Furthermore, even if the skilled person were motivated to re-plate the cells, there is absolutely no teaching or suggestion in Nishikawa that would lead a person of skill in the art to change the culture conditions under which the iteratively divided cells are grown. Nishikawa is directed towards the production of specific cell types in 2D culture, not to the regulation of cellular processes through modulation of culture conditions and so would not provide a motivation for the skilled person to undertake any such experimentation. In fact, one

of ordinary skill in the art would be taught away from changing the culture conditions as Nishikawa indicates that the conditions disclosed in Nishikawa are effective.

Accordingly, claims 1 and 2 and claims that depend therefrom are patentable over Nishikawa. Applicants respectfully request that this rejection be reconsidered and withdrawn.

Scholl

The Examiner has rejected claims 1, 2 and 4-16 under 35 U.S.C. § 103(a) as being anticipated by U.S. Publication No. 2004/0170965 to Scholl et al. ("Scholl"). See Office Action at p. 45. Claim 4 was previously cancelled thus rendering this rejection moot with respect to claim 4. Claims 5-16 depend from independent claims 1 and 2.

With regard to Scholl, the Examiner has cited Example 1 (paragraphs 147 to 154 of Scholl) as rendering the current claims as unpatentable over Scholl. See Office Action at p. 5-6. The Examiner states that those passages disclose culturing cells to confluency in sterile flasks containing medium supplemented with various additives. See Office Action at p. 5. Scholl also discloses that cells were harvested by rinsing with Hank's Balanced Salt Solution (HBSS) and then dissociated by the addition of trypsin. See paragraph [0149] of Scholl. The cells were further diluted to a specified optical density and then cell mixture monolayers were produced by co-planting two distinct cell types at an equal volume of each diluted cell suspension. See paragraphs [0149]-[0150] of Scholl. The ability of the cells to grow in mixed monolayers was assessed for the ability of these cell lines to co-exist and develop as a single cell sheet. See paragraph [0151] of Scholl.

In relation to the methods described in claims 1 and 2, it is firstly submitted that a person of ordinary skill in the art would have no motivation to view Scholl when looking to identify methods for determining the effect of a plurality of culture conditions on a cell since Scholl is directed towards an entirely different field of the art, namely compositions and methods for detecting and differentiating one or more viruses or other intracellular parasites present in a specimen. See abstract of Scholl.

Secondly, in relation to claim 1, Scholl does not disclose all of steps (a) to (c), or step (d) of repeating the steps iteratively. The same argument applies in relation to the steps described in claim 2. In viewing Scholl, it would be apparent to one skilled in the art that the cells which must be considered to be the first set of groups of cells of step (a) which are exposed to desired

culture conditions must be those cells which have been washed and trypsinized to provide a cell suspension as described in paragraph [0149] of Scholl. However, the Examiner's attention is again drawn to the fact that the methods described in claims 1 and 2 are directed towards methods of determining the effects of a plurality of culture conditions on a cell. It is submitted that the act of initially growing any given cells to confluency so that they can be used in a further cell biology method cannot be considered to form part of the method as described in claims 1 and 2. This is because this step does not relate in any way to determining the effect of the culture conditions on a cell, and is undertaken to merely expand the number cells present for subsequent use.

The method disclosed in Scholl can therefore only be considered to involve a single step of exposing the cells to desired culture conditions, equivalent to step (a) of the clamed methods. Thus, Scholl does not disclose the step of subdividing the groups of cells which have previously been exposed to desired culture conditions and the exposure of such cells to at least one change of culture conditions. In light of this, Applicants submit that even if a person of skill in art would be motivated to use or modify Scholl, there is nothing which would lead one of ordinary skill in the art to modify the methods disclosed in Scholl to arrive at the methods described in claims 1 and 2. It is submitted that any other conclusion can only be drawn by an impermissible hindsight analysis of the methods disclosed in the present claims and an incorrect analysis of the method steps as claimed in independent claims 1 and 2.

Thirdly, even if the Examiner does not agree with Applicants' arguments as set out above, Applicants respectfully submits that contrary to the Examiner's assertion, it would not be obvious to one of ordinary skill in the art viewing Scholl to amend Scholl's teaching to iteratively subdivide the cultured cells to form further groups of cells and expose these cells to at least one change of culture conditions. As indicated by the Examiner, the method described in Scholl is directed towards the production of mixed cell monolayers having approximately equal densities of each cell type (see Office Action at p. 5 and 6). A person of ordinary skill in the art would understand that if these mixed cell monolayers were subdivided and replated then the ratio of cells would in all probability alter resulting in monolayers having very different ratios of cell types. Therefore, it is submitted that this would not result in a highly efficient outcome and would in fact render the method entirely inefficient. In fact, one of ordinary skill in the art viewing Scholl, would consider that it would be undesirable to iteratively repeat subdivision and

culture of the cells. This would merely result in more samples of questionable worth and therefore more work, which one skilled in the art would consider to be unnecessary in light of the fact that it is indicated that the methods disclosed in Scholl are already effective for the purposes of Scholl.

Finally, there is no teaching or suggestion in Scholl which would lead the skilled person to modify the teachings of Scholl such that in each iteration of cell culture, at least one culture condition was changed.

As such, Scholl does not teach or suggest a method for determining the effect of a plurality of culture conditions on a cell that includes the steps of: (a) providing a first set of groups of cell units each including one or more cells, and exposing the groups to desired culture conditions, (b) subdividing one or more of the groups to create a further set of groups of cell units, (c) exposing the further groups to at least one change of culture conditions, (d) repeating steps (b)-(c) iteratively and (e) assessing the effect on a given cell unit of the culture conditions to which it has been exposed. Scholl further does not teach or suggest a method for determining the effect of a plurality of culture conditions on a cell, that includes the steps of a) providing a first set of groups of cell units each including one or more cells, and exposing the groups to desired culture conditions, (b) pooling two or more of the groups to form at least one second pool, (c) subdividing the second pool to create a further set of groups of cell units, (d) exposing said further groups to at least one change of culture conditions, (e) repeating steps (b)-(d) iteratively and (f) assessing the effect on a given cell unit of the culture conditions to which it has been exposed.

Accordingly, claims 1 and 2 and claims that depend therefrom are patentable over Scholl. Applicants respectfully request that this rejection be reconsidered and withdrawn.

CONCLUSION

Applicant believes that the claims are in condition for allowance. Should any fees be required by the present Reply, the Commissioner is hereby authorized to charge Deposit Account 19-4293.

Respectfully submitted,

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